EFED POLICY MEMORANDUM

SUBJECT: Use the NOAEC from Aquatic Chronic Toxicity Tests in Risk Assessment

FROM: Denise M. Keehner, Acting Director
Environmental Fate and Effects Division

TO: EFED Staff

Overview

It is the EFED policy that the NOAEC from chronic aquatic or estuarine toxicity testing will be used for assessing chronic risk to aquatic and estuarine animals. This includes the *Daphnia magna* 21-day life cycle test, the fish early life stage test, the fish full life cycle test, and the shrimp life cycle test.

Background

The Aquatic Biology Tech Team (ABTT) proposed, and the Science Policy Panel (SPP) concurred, to modify the former EFED policy for deriving the chronic toxicity endpoint for assessing risk to aquatic organisms. The previous policy advocated using either the NOAEC or a theoretical MATC (geometric mean of the NOAEC and the LOAEC) depending on the observed effects at the LOAEC. If reproduction or survival effects occurred at the LOAEC, the NOAEC was to be used, however, if the effects were to growth only, the MATC was to be calculated and used. The Aquatic Biology Tech Team proposed that the NOAEC always be used and provided several supporting reasons why they thought this was appropriate. These arguments are included as attachment I. The Science Policy Panel reviewed the Aquatic Biology Tech Team's proposal, and recommended that proposal be adopted. See attachment II. The EFED management agrees with the proposed policy change and appreciates the significant effort by both the ABTT and the SPP that went into this proposal.

Discussion

The NOAEC is the highest test concentration at which none of the observed results were statistically different from the control. The LOAEC is the next higher test level, and the one at which one or more observed results were statistically different from the control. The MATC is considered to be somewhere between the NOAEC and the LOAEC and sometimes is presented as a concentration calculated by taking the geometric mean of the NOAEC and LOAEC. Statistically, the effects at this calculated MATC might be significantly different from the control.

In EFED risk assessments, the NOAEC is to be used as the toxicity threshold for chronic risk screens. The tests mentioned above, as currently designed, are intended for hypothesis testing rather than for the determination of a dose-response relationship. The extent or magnitude of chronic risk cannot be quantified with the results from the current aquatic tests. Exposure below the NOAEC level is presumed not to be a significant risk, while exposure exceeding the NOAEC is presumed to represent a chronic risk.

Neither a calculated MATC nor the LOAEC are acceptable endpoints for chronic risk assessment. While they would allow a conclusion of risk if exposure exceeded either one, neither would allow a conclusion of minimal risk if exposure were less than either, but still greater than the NOAEC.

Attachment III provides a discussion of the impact this policy decision would have on risk assessment conclusions.

ATTACHMENT I

U. S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM **DATE:** February 16 ,1999

SUBJECT: Use of the NOAEC versus MATC in Chronic Aquatic Risk Assessments Determinations

FROM: The Aquatic Technical Team
Environmental Fate and Effects Division

THROUGH: Aquatic Technical Team Co-chairs
Thomas M. Steeger, Fishery Biologist
Brian Montague, Fishery Biologist

TO: Mary Frankenberry, Chairperson
Science Policy Panel
Environmental Fate and Effects Division

The Aquatic Biology Technical Team (ABTT) has reviewed the rationales regarding the use of the no-observed-adverse-effect concentration (NOAEC[1]) versus the maximum allowable (acceptable) toxicant concentration (MATC[2]) as the most reasonable means for deriving sublethal continuous data and chronic toxicity endpoints for fish and aquatic invertebrates. The ABTT believes there are compelling reasons to use the NOAEC *en lieu* of the MATC. These reasons are presented to the Science Policy Panel for consideration in establishing a uniform policy on which chronic aquatic toxicity endpoint should be used in calculating hazard (risk) quotients.

From the perspective of the ABTT, the NOAEC is the preferred value to be used in chronic aquatic risk assessment for the following three reasons.

1. Potential for manipulation of the MATC by study design.
2. The NOAEC represents an empirically derived point where no statistically resolvable effects

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[1]NOAEC: the NOAEC (NOEL) can be defined as the highest test material concentration that causes no statistically significant difference from controls in organismic response (Payne and Hall, 1979). For the purposes of this memo, the no-observed-effect level (NOEL) and the NOAEC are considered synonymous since any statistically significant effect, i.e., statistically different from controls, would be viewed as ecologically adverse. The use of the NOAEC is in compliance with a memo from Ms. Marcia Mulkey.

[2]MATC: the hypothetical toxic threshold concentration lying in a range bounded at the lower end by the highest tested concentration having no-observed-effect (NOEC or NOAEC) and at the higher end by the lowest tested concentration having a significant toxic effect (LOEC or LOAEC) (Rand and Petrocelli 1985; Tyler and Schroeder 1979; Mount and Stephen 1967)).

occur; exposures at or below this concentration will not result in biologically significant effects to species of similar sensitivities. However, the MATC is an arbitrarily-derived estimate without direct empirical evidence to support the contention that biological effects associated with the lowest observable effect concentration would not occur.

3. The NOAEC does not represent a "no effect threshold" and that minimal adverse effects are still likely to occur at this level.

The ABTT believed that it was unreasonable to utilize the MATC since it potentially represented even greater uncertainty and thus was less conservative than the NOAEC. The uncertainty in the NOAEC was further characterized as resulting from the following factors:

- The NOAEC is a standard estimate that may not necessarily reflect interspecies differences. There are over 2,000 species of freshwater and saltwater fish in North America and tens of thousands of aquatic invertebrates, but only several common species serve as indicator species in our toxicity tests (Hazard Evaluation Division, Standard Evaluation Procedure, Ecological Risk Assessment, EPA-540/9-85-011)
- The NOAEC may not reflect the longer term multi-generational exposures.
- The NOAEC for growth and reproductive effects may not reflect other equally important chronic effects which are not measured in our current guideline study designs.
- Present testing methods do not duplicate environmental stressors, other than pesticides, that may lower chronic thresholds.

The rationales presented here are further discussed in Attachments. For further questions, please contact Tom Steeger or Brian Montague, ABTT Co-chairs.

Attachment A

Rationales for the Use of NOAEC as Aquatic Chronic Toxicity Endpoint

Prepared by Dr. Edward Odenkirchen, Dr. Thomas Steeger, and Mr. Brian Montague for the EFED Science Policy Panel on behalf of the EFED Aquatic Technical Team

- **Potential for manipulation of MATC by study design**

Both the NOAEC and the LOAEC[3] (lowest observed adverse effect concentration) are statistical estimates dependent on the limits of statistical confidence and the selection of the dose progression used in the study. Unless limits are set on the maximum effect level permitted to be assigned to the LOAEC point for MATC computations, widely separated doses at the lower limits of a dose progression will result in inflated estimates of the MATC.

Selection of the NOAEC as the toxicity threshold value could result in the selection of more numerous dose intervals on the low-end of the dose progression by the testing laboratory. Encouraging selection of additional dosages near the lower-end of the curve may serve to elevate the NOAEC and perhaps move it closer to the LOEC.

- **NOAEC is the product of direct observation.**

The NOAEC, by definition, is the result of direct observation of a set of test replicates. EFED has data for each toxicity test, that demonstrates for a defined set of biological parameters, that no statistically significant effect was noted at the NOAEC. In contrast, there are no data, i.e., no direct observations, to support that the MATC has any effect associated with it. Suter (1990) has noted that the MATC represents an arbitrary estimate of an effect threshold that might lie anywhere in the range defined by the NOAEC and the LOAEC. It is only assumed that the true effect threshold is well approximated by the MATC.

- **Even the NOAEC is unlikely to be conservative.**

A common regulatory approach to dealing with uncertainty in risk assessment is the selection of the more conservative estimate (parameter value) to allow for some element of safety in assessing risks. Ironically, the historical approach for establishing "acceptable"levels of exposure for chemicals that exhibit adverse effects in a "threshold" manner has been to reduce the NOEL by a safety or uncertainty factor that considers both intraspecies and interspecies differences (Klaassen and Eaton 1991). The NOAEC is in all cases more conservative than the MATC. However, in deciding which is more appropriate for EFED's purposes, the potential conservatism of the NOAEC should be considered. The current statistical evaluations of data usually consider a confidence level of 95% ($\alpha = 0.05$) as the acceptable probability of a Type I statistical error, *i.e.*, the false conclusion

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[3]**LOAEC:** In general, the Division has equated this data point as the concentration at which measured parameters show a 5% observed difference from the control groups as statistically verified through use of ANOVA, contingency tables, or other hypothesis testing procedures.

that a treatment concentration is toxic. Historically, environmental researchers have focused on the Type 1 error and have largely ignored the probability of making a Type II error (β), i.e., the probability of erroneously concluding that there are no statistical differences between a control and treatment group. In EFED's current testing guidelines, the limited number of true replicates effectively increases the probability (β) of Type II errors and limits the power (1 -β) of the bioassay.

Fairwether (1991) discusses the consequences of Type I and Type II errors as follows: "The commitment of time, energy, and people to a false positive (a Type I error) will only continue until the mistake is discovered. In contrast, the cost of a false negative (a Type II error) will have both short- and long-term costs (*e.g.*, ensuing environmental degradation and the eventual cost of rectification)." In this light, it is prudent to adopt the more conservative NOAEC instead of the higher MATC.

- **The NOAEC is a conservative estimate that may not necessarily reflect interspecies differences.**

There is a potential for considerable variability in the NOAEC among different species. The resulting NOAEC does not account for intra- and interspecies differences and may, like Klaassen and Eaton (1991) have suggested, require an uncertainty factor be applied to reduce the NOAEC. Given the uncertainty in the conservatism associated with the NOAEC, it is unlikely that these concerns would be adequately addressed by upscaling the chronic toxicity threshold through use of the MATC.

- **The NOAEC may not reflect the longer term multi-generational exposures**

Fish early life stage and life cycle testing for invertebrates may not reflect the potential time of exposure for extremely persistent chemicals. With extended exposure times lowest effect concentrations may decrease and with this decrease a shift in the maximum acceptable toxic concentration range. Most of the studies used for determination of chronic effect to fish are indicative of partial chronic toxicity only since it includes only a portion of the organism's full life cycle. Only 29 of the over 600 active ingredients have full life cycle testing data for fish. Thus, use of the lower early life stage concentration (NOAEC) may be more protective for fish species for which no full chronic data is available.

- **The NOAEC for Growth and Reproductive Effects may not reflect other equally important chronic effects levels which are not tested**

Use of the higher point estimate (geometric mean of NOAEC-LOAEC range) would afford less protection from untested parameters which might occur at lower dose levels. For example it is suspected that many recognized endocrine disruptors would pass present chronic safety screens.

- **Present Testing Methods Do Not Duplicate Environmental Stressors that may Lower Chronic Thresholds**

The American Institute of Biological Science has indicted this factor in their Criteria and Rationale for Decision Making in Aquatic Hazard Evaluation. They state that " laboratory tests may predict too high of a MATC value for safety in the environment since test organisms are not subjected to the same stresses of disease, predation, deprivation, alterations in environment, etc. Such stresses experienced by wild populations may alter their ability to tolerate pollutant pressure." To raise the decision endpoint would serve to exacerbate this possible difference.

References

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ATTACHMENT II

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM April 14, 1999

SUBJ: Policy on the Use of the NOAEC in Toxicity Testing for Chronic Effects in Aquatic Animals

TO: Denise Keehner, Acting Director
Environmental Fate & Effects Division 7507C

FROM: Mary Frankenberry, Chair
EFED Science Policy Panel

The Science Policy Panel has reviewed the proposal from the Aquatic Biology Technical Team for using the No Observed Adverse Effect Concentration (NOAEC) in establishing chronic toxicity endpoints for aquatic species. The Panel agrees with the Tech Team that the NOAEC should be used, rather than the MATC (Maximum Allowable Toxicant Concentration), in establishing endpoints for sublethal and chronic effects in fish and aquatic invertebrates.

The OPPTS Draft Test Guidelines for Ecological Effects (1996) defines the NOAEC as the "highest concentration of a material used in this test (daphnid chronic toxicity) that does not have an adverse effect on the test organisms and is the test concentration immediately below the LOAEC." The attached memo from the ABTT references a similar definition and lists several rationales in support of its use. The Science Policy Panel believes that most salient among these are the option for a more protective endpoint measure, in addition to the choice of the NOAEC as an empirically derived point against which to compare estimated concentrations. While the MATC is a calculated value, the NOAEC is the highest test material concentration that causes no significant difference in response between test and control animals. As such, it will always be a lower bound for the range containing the MATC calculation.

Other rationales are discussed in the Tech Team memo. They address the uncertainty associated with extrapolating results across species, from laboratory to the field, from one effect to another, and from one generation to another. The Science Policy Panel believes that the discussion of uncertainty is an essential element of the risk characterization for any chemical. As such, it should be addressed in a separate section of the RED document for every chemical for which risk is assessed. EFED staff are referred to Attachment A of the ABTT memo for a good discussion of these major sources of uncertainty and for further references.

cc: EFED Branch Chiefs

Science Policy Panel Members
Thomas Steeger
Brian Montague

Attachment III

Impact of this policy on Risk Assessment Conclusions

This change in policy will have moderate effects on the magnitude of risk quotients, *when it changes the risk at all.* Note that in cases where the effects at the LOAEC were to survival or reproduction, the policy was to use the NOAEC anyway, so the resulting risk quotient would be the same.

In most cases where based on the effects at the LOAEC, the MATC would have been calculated and used in aquatic risk assessment, the numerical difference between NOAEC and the MATC would usually be less than a factor of two. In other words, the MATC would not even be 2 times greater than the NOAEC; or put another way, the NOAEC would not be less than one half the MATC. Assuming the test concentrations in the study are not more than a factor of two apart the MATC between any two of the test levels would be approximately 1.4 times the NOAEC. Concentrations for aquatic chronic studies are usually not further apart.

For example, if the NOAEC is 1 ppb, and the LOAEC is 2 ppb, the MATC (geometric mean) is1.4 ppb. Therefore, risk quotients calculated from the NOAEC would not be more than 1.4 times higher than those calculated using the MATC. The only difference to actual LOC exceedences would be if the risk quotient from the NOAEC exceeded the LOC by a small margin, e.g. 1.2. Then the risk quotient from the MATC would have been slightly lower than the LOC.

The following hypothetical example shows the difference in the magnitude of the risk quotient at various exposure levels, and at what point, relative to the EEC, it would make a difference *in LOC exceedence* whether the NOAEC or MATC was used.

NOAEC=1 ppb
LOAEC=2 ppb
MATC=1.4

EEC	50	25	10	3	1.7	1.3	1	0.8
RQ (NOAEC)	50	25	10	3	1.7	1.3	1	0.8
RQ (MATC)	35	17	7	2.1	1.2	0.9	0.7	0.6
LOC exceeded? NOAEC/MATC	yes/yes	yes/yes	yes/yes	yes/yes	yes/yes	yes/no	yes/no	no/no